Dietary zinc and bio-function mini-review

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Introduction

Zinc deficiency is one of the most wide-spread micronutrient deficiencies in plants and causes severe reduction in crop production, thus creating human dietary deficiency in both underdeveloped and developed countries. The World Health Organization (WHO) presented mortality attributable to selected leading risk factors (Fig. 1). Obviously blood pressure, smoking (mostly in males), choresterol, and underweight (malnutrition) are major factors, but unsafe sex, fruits and vegetable intake and alcohol consumption (only in males) should also be noted. Some environment-related factors, like physical inactivity, hygiene and from solid cosmetics (higher in females) are also noticeable factors. What we should not ignore is that deficiencies of iron, zinc and vitamin A which are leading risk factors in both sexes.

Our health and physical condition depends on what we eat and how we behave every day. Thus, the intake of dietary zinc and the trouble caused by its' deficiency must be carefully examined. As we know, the intake of inorganic zinc is inefficient but intake through fruit, vegetables and other biological material in organic form is more effective. Here we will consider first how and where zinc is utilized in plants, followed by it's nutritional value to our body.

A soil survey showed a generally lower content of zinc in Japanese soil, relative to average earth land and thus vegetables with a lower zinc content are served on the table. Modern agriculture uses various fertilizers but most of them are rich in nitrogen, phosphate and potassium but not in minerals. Zinc is indispensable in various metabolic pathways and physiological functions in most plants and animals including human.

Zinc stimulates immune function

Deficiency of zinc is known to cause various abnormal conditions, from dwarfism with extremely short life-span and parasite infection to micro-organism attack. What is happening in the case of mild zinc deficiency? A semi-purified diet based on texturized soy protein was prepared for consumption by human volunteers. The subjects consumed a hospital diet containing animal protein daily for 4 weeks. Then, they were supplied with or without 3 to 5mg zinc per day. The experiment continued for 28 weeks after which the subjects received 27mg zinc per day as a supplement for 12 weeks together with the hospital diet. Throughout the study, the amount of all nutrients was kept constant except for zinc. The following results were observed: Serum thymulin, a thymus-specific hormone, activity increased. Thymulin binds receptors on T cells with high affinity and promotes their immune function, including allogenic cytotoxicity, suppressor functions , and IL-2 production [1]. As a result of mild zinc deficiency, thymulin in serum decreased significantly and the subjects became sensitive to various infection. The natural killer (NK) cell activity was also sensitive to zinc

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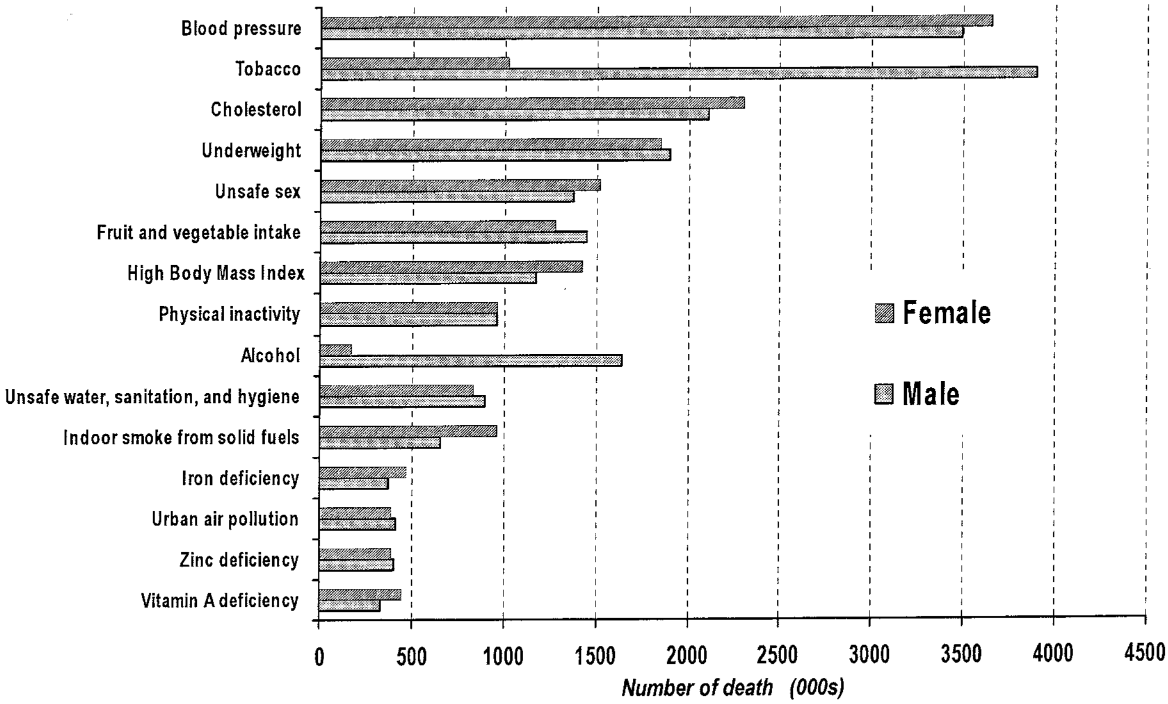

Fig. 1. World Death in 2000 attributable to selected leading risk factors, by sex.

restriction[2]. Production of IFN-γ was decreased, while some other IFs maintain their levels [3].

Even a mild deficiency of zinc induces an imbalance of the immune system, especially through redution of thymulin. Inversely, zinc is essential to protect our health.

Antioxidant effect of zinc in humans

Oxidative stress is known as an important contributing factor in many chronic diseases. In healthy normal subjects, zinc acts as an effective anti-inflamatory and antioxidant agent. Voluntary subjects receiving zinc showed a decreased plasma levels of lipid peroxidation products and DNA adducts while no change was observed in a placebo group. In studies using cell lines, zinc enhanced the upregulation of mRNA and DNA-specific binding for A20, a transactivating factor that inhibits the activation of NF-κB. These suggest that zinc supplementation may lead to downregulation of the inflammatory cytokines through upregulation of the negative feedback loop A20 to inhibit the induced NFκB activation and to promote anti-inflamatory and antioxidant effect *in vivo*.

Higher quality of health in elderly with zinc

A study group using elderly subjects (age 55-87) who were free of any significant chronic diseases and ambulatory and active, was divided into sub-groups with or without zinc supplement. 15 mg of zinc gluconate in capsule-form was given orally 1 hour before breakfast and 2 hours before going to bed for 12 months. Half of them were given a placebo. A nurse practitioner evaluated subjects who appeared to have infections, and laboratory variables were measured, to see the generation of cytokinins, and oxidative stress markers. A comparison of baseline data between young adults (age 18-54) and elderly subjects shows that, plasma zinc decreased, and the percentage of cells producing

IL-1β and TNF-α and the levels of these cytokinines increased. Also, oxidative stress markers increased in the elderly. This suggests the higher sensitization and stronger stress were generated in the immune systems of elderly subjects [4].

The beneficial effects of zinc in the management of infantile diarrhea and acute respiratory infections in children in the developing world, as evidenced by decreased mortality, morbidity, and incidence of infections in parents with sickle cell disease and the elderly subjects, are due to the important roles of zinc in cell mediated immune functions [5]. Zinc has been used as an antioxidant for treatment of age-related muscular degeneration for the past 10 years with successful results preventing blindness in many patients, and significantly decreasing mortality among zinc-treated subjects.

Zinc plays an important role in cells by increase immunity and as an antioxidant agent but also in the prevention and cure of many chronic diseases such as atherosclerosis, cancer, neurodegenerative disorders, rheumatoid arthritis, and even aging. Zinc may prove to be an useful chemo-preventive agent as long as given orally with balanced and nutritional diet.

Zinc in natural and local foods

The content of zinc in soil varies and the content of zinc in plants depends on the soil where they grow. In some regions, despite a high content of iron, magnesium, calcium and other minerals, zinc availability is limited. If zinc content in vegetables and fruits, is limited, animals including human raised on these will face a shortage of zinc for maintaining an active life.

The average adult male and female require 12-15mg and 10-12 mg of zinc every day, respectively. When a woman practices dieting, it may decrease to 6 mg/day. Such reduction of zinc intake in laboratory animal increases the amount of free radicals by 15-20 percent. A shortage of zinc has been found in 60% of dementia patients, suggesting zinc may be a factor for prevent neurological degeneration. It also soon causes an abnormal taste sansation. The cells in our taste buds metabolize quickly with a less than 10 day interval. This creates an abnormal preference towards certain foods. More than 300 enzymes and proteins contain zinc and no one can underestimate the importance of zinc in foods.

Enriching the zinc content in various plants has been successfully tested in grass, soy bean, carrot[6] and rice[7] by supplying zinc chloride solution or Sado deep sea water. When these plants were supplied with 1 mM zinc chloride solution, the content of zinc in tissues increased from two to twenty times depending on the plant and organ. The highest percentage of increase, compared with plants grown in tap water, was found in carrot root (20 times) followed by leaves of grass (10 times) and fresh green soy bean seeds (measured after boiling, with a bit of salt). Rice grains given with extra $ZnCl_2$ contained a little more than 3 times of the level zinc over usual rice grown in paddies. Grasses tested were young corn and Sudan grass and grown as a feed for animals. Those animals given zinc rich grasses produce healthier milk, healthier off-spring and, thus, a healthier society in Japan..

Zinc enriched rice has a taste as good as commercially produced first class varieties and thus it may contribute to our health. With respect to high content of zinc to human, except in gaseous form, the toxic concentration of inorganic zinc is 0.01 to 0.03% (w/w) as water solution, which causes chlorosis (a loss of chlorophyll and/or total chloroplasts) in plants and suppression of growth in both in plants and animals. Such high concentrations never occur in living animals, and thus, one can say that zinc accumulation in foods will never harmtul to organisms. Rather, a suitable concentration of zinc prevents oxidation of SH groups and reduces stress in living organisms.

We have found that Sado deep-sea water contained relatively higher concentrations of zinc besides other minerals. Thus providing deep-sea water in place of zinc solution is useful, because many other useful minerals are also available. Both desalinated and 20-fold times diluted deep sea water are usable to increase zinc content by factors of 10 to 20% in the plant organs mentioned above. Under normal conditions use of sado deep sea water may help people with minor deficiency of zinc. Whichever form of zinc, either the solution or deep-sea water, desalinated or diluted, will supply zinc to our vegetative foods. Zinc included in plants will act to maintain our health through various metabolic pathways.

It has been noticed that invasion of sea water over coastal agriculture land, due to a flood brought by storm, sometimes gives us a better yield of fruits and crops. Sun-Hee Hong and his group (Wuhan, China)[8] successfully transformed japonica rice capable to yielding 22-25% more under the stress condition induced by dryness and salt water invasion. This rice produced as good a grain as regular rice grown under the normal condition. They reported the function of special transcription factors, such as NAM, ATAF, CUC(NAC), to produce salt- and dryness-resistant proteins. Environmental stress, such as dryness, salt and heavy metals induces an accumulation of superoxides inside of cells. Organisms resistant to such stress begins to produce anti-oxidation systems, including copper/zinc superoxide dismutase (CDS1 and CDS2). Induction level of these enzymes are controlled by mi398 (micro-interference RNA). Under normal conditions, mi398 breaks down mRNA of CDS1 and 2, suppressing the production of these enzymes, but under stress mi398 production stops and then, CDS1 and 2 increase anti-oxidation. Interestingly, some plants with strong anti-stress ability have anti-mi398 CDS2.

Some zinc rich foods are the following: Oyster, clams, various red meats, some insects and various beans. These are also rich in iron, calcium, magnesium and other minerals found in sea water. Iron deficiency, a major factor of the anemic condition, can be cured by zinc supply, when supplying iron tablets does not work. One must note that polyphosphates, carboxymethyl-cellulose and EDTA remove zinc from inside of cells, and phytic acid, often rich in beans, disturbs zinc uptake under the presence of calcium.

Zinc in bottled tea and soft drinks

Zinc has been recognized as an indispensable component as well as a health promoter in human and zinc supplementation (0.1mg/100ml for example) is becoming popular in today's society. Such materials also include magnesium (0.5mg), potassium (18mg), phosphate (1.0mg) and manganese (3.0μg) in 100ml. Unfortunately, zinc is rarely mentioned in Japan because ① zinc in kanji character means sub-lead where lead is known as a potent and persisting poison and ② the importance of zinc in physiology has generally been ignored except among scientists. Often components like sodium, magnesium, calcium, potassium, phosphate and iron (Table 1) are indicated as ideal minerals in water but zinc is seldom mentioned. Water, rich in minerals, is preferred in Europe and low mineral content water is preferred in Japan for drinking. Hard water makes all tea (green or black) unacceptable because of color change, but has much less effect in coffee.

Some bottled water is collected from wells and others from springs and stream in the deep mountains. Some others are prepared from deep sea water pumped up from 300 meters or deeper. Deep sea water is formed by cold temperature near the pole. Because of it's higher density brought about by chilling effect of extremely low temperatures, it sinks into deep sea where organism and micro organism can seldom survive. Such chilled deep sea water slowly moves away from the pole, as the next group of sea water is chilled and sunk, to be pushed away from poles. Such sea water is clean and safe to use and to store for long periods. Chemical analysis has shown that deep sea water is rich in minerals wherever it is pumped up in Japan, Okinawa, Kochi (both are on the Pacific side), Toyama, Sado island (both are on the Japan sea side) and Hawaii, U. S. A. The concentration of constituents including minerals varies due to location. Deep sea water pumped up from a depth (＞300meters) is passed through a nano-membrane to remove micro-components followed by reverse osmosis and/ or ion column using direct current to separate sodium from other constituents. This column system helps to enrich certain ions. Thus, separated and/or desalinatedd deep sea water can be used for drinking, cooking various foods, fermentation to make “miso”, “shoyu” and “sake”, as well as in agriculture, to raise livestock and to produce milk.

Zinc controls brain system through neuro-peptide Y

Although the real reasons for lack of appetite varies, the involvement of minor minerals is certainly one of many factors. A shortage of zinc has been noticed in many cases of neurotic anorexia. The content of zinc excreted into urea was less than half of the healthy control subject. Feeding of zinc has increased the zinc in serum and urine as they gain weight and activity, but not in case of placebo. Further, levels of lactic dehydrogenase and alkaline phoshatase activities, both zinc-containing enzymes, were reduced by 21% and 38% respectively. In laboratory experiments using young rats, feeding of low zinc food for 3 to 5 days reduces their appetite, and feeding of no zinc containing food reduces food consumption to less than 50%. The reduction in eating came from reduced appetite for carbohydrates and was easily reversed within a day by supplying zinc. This means that zinc effects appetite but also nutritional selection. Zinc also affects the timing of eating. Normally, rats start to eat as soon as it becomes dark but zinc deficient animals delayed to start their feeding.

Neuro-peptide Y (NPY) is found, rather in a large quantity, in the central nervous system including cortex, thalamus, amygdala, hypocampus, and a significant amount in peripheral nerves, and controls a wide variety of functions, including reproductive behavior, circadian rhythmus, circulation, memory and stress reaction. If NPY is introduced into the central system, it stimulates the animal's appetite. NPY in the hypothalamus increases during starvation and stimulates the appetite for carbohydrates. These suggested some relation between anorexia caused by zinc deficiency and NPY production. Later, it became clear that transcription of NPY gene was stimulated but translation seemed to be hampered. Zinc deficient effects could be suppressed by the receptor(s) of NPY. However, the fact that an introduction of NPY stimulates appetite, suggests the presence of functioning NPY-receptor. An other possibility remaining is an inhibition of produced NPY from the production site of nerve system(s). Nevertheless, zinc is indispensable for normal neuro-function[9)].

Uptake, export and transport of zinc

Zinc transport (ZnT) protein consists of a group of membrane-bound proteins and passes through the cellular membrane six times, and it has a group of intra-cellular segments containing a histidine rich chain where the zinc ion binds. Four kinds of ZnT as family exist in mammalian cells to control the contents of zinc through uptake and excretion. ZnT1 and ZnT-2 mRNA are found in small intestine, kidney and placenta cells and arelocated on the surface of cellular vesicles to transport zinc to and from cellular membranes. ZnT-3 localizes in the testis and brain. ZnT-4 mRNA found in small intestine, kidney and liver are not effected by zinc, suggesting their role for storage control. It is found also in lactate glands during breast feeding.

The other zinc transporter is Zip family. expected to work on the inflow of zinc. Three genes hZip1, hZip2 and hZip3 have been sequenced and introduced into K562 cells. Uptake of zinc by these transformed cells increased two fold. These hZip transporters are located on cell membranes and are absent in cells.

Studies on where absorption of zinc takes place in human body are scarce, relative to those on calcium and iron. Calcium is absorbed in the duodenum by active transport and in the jejunum by passive transport. For intestinal heme absorption, the duodenum is a major site of absorption, and it is where some specific heme carrier protein (HCP1) are produced by transcription and translation. Transfection of Hcp1 gene increases absorption of heme, tested by fluorescent analog. An HCP1-specific siRNA abolished the HCP1-induced increase of heme uptake, while and HCP1-specific antibody inhibits iron absorption in intact duodenum. In another study, HCP1 mRNA levels are strongly induced by hypoxia but not by alteration of iron storage; gene involved in none-heme iron transport, in contrast, are highly regulated by the storage of iron. Different mechanisms may have evolved to deal with inorganic iron and heme[10). Although more research is needed for zinc transport, it may be most likely that zinc is also absorbed and transported in small intestinal cells through receptors in cellular membrane.

Current diet and zinc

In the United States of America, diet supplies 77% of calcium, 56% of zinc, 19% of iron, 16% of cupper and 29% of magnesium、mainly from animal products. When diet changes to a vegetative source, we should be concerned about iron and zinc supply. Plant foods, high in zinc content, like soybean, grain, seeds and tree fruits, also contains high amounts of phytic acid. Although phytic acid is considered to be an anti-carcinogenic phytochemical, it is also an inhibitor of zinc uptake and its' function. Many fresh plant foods contain phytic acid which reduces efficiency of absorption of zinc, but vegetables and crops are more useful after treatment/cooking than purified or manufactured ones. For example, whole grain bread and white bread show absorption efficiencies of 16.6% and 38.2% but total content of zinc are 1.3 mg and 0.22 mg, respectively and thus their. absorption of zinc at final are 0.22mg and 0.15 mg, respectively. Whole grain bread is better source of zinc. WHO[11)] documents the biological utilization of zinc with high value (absorption rate 50-55%), medium value (30-35%) and low value (15%) from animal protein, combined diet and vegetarian diet, respectively. The more plant materials are in the diet, the lower amount of zinc supply is available. Also, increased intake of phytic acid, is observed especially with calcium fortified plant materials. People concerning plant foods may have a shortage of zinc unless zinc rich vegetative foods are chosen to replace meat. When meat was replaced by plant food, zinc intake will be 13 ～ 6.7 mg/day. For woman in menopause, zinc intake will be reduced from 3.6 to 2.0 mg/day, even if the zinc absorption rate remains at 29%. Thus, they should concerned about uptake of zinc. Vegetarian diet can easily create a lack of zinc as mentioned above. Current trends in low calorie diet must be reconsiderde considered carefully.

Never the less, no satisfactory method for quantification of zinc in various parts of the body, especially, zinc in blood, skin, bone and hair exists and then exact values should be determined for better evaluation of zinc function. Meantime, lower meat intake and a more vegetalian diet must be carefully examined by dieticians.

Conclusion

A lower content of zinc in most of the land in

Japan is affecting the zinc content of various food plants and secondary products like eggs and milk. A chemical form of zinc is obtainable commercially at low cost and from deep sea water in form of combined minerals. Zinc makes contributions to be immune reaction and various control mechanisms including ageing, pregnancy and growth and development like calcium, magnesium and other important minerals. The function of zinc remains to be further studied, as our diet changes with age, social status and health perceptions.

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